Medical Progress

Recent Progress in Calcium Metabolism: Clinical Application

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"Those who do not know the past are condemned to relive it."—Santayana

IN THE LAST DECADE accurate calcium determinations, once found only in highly specialized research laboratories, have become generally available. As a result, the practicing physician is often confronted with minor deviations from normal which he must assess. Hyperparathyroidism, once thought rare, is recognized with increasing frequency. This technological advance has been accompanied by similar progress in scientific knowledge. Copp's[1] clarification of the factors responsible for the precise control of calcium homeostasis has added a new dimension to physiology and pathophysiology. DeLuca's[2] brilliant demonstration of chemical activation of vitamin D, and Avioli's[3,4] elucidation of the role of this process in health and disease, have added considerably to our understanding of disturbed calcium metabolism. Not surprisingly, clinicians have quickly sought therapeutic applications of these discoveries. The time seems ripe to review this recent progress and to reexamine previous information in the light of new developments.

Since this review is primarily clinical in scope, many important basic scientific contributions—such as the role of cyclic adenosine monophosphate (AMP) in parathyroid hormone action—the clinical applications of which are not yet clear, are not included. By the same token, important clinical problems for which there is no clue to solution—for example, endocrine adenomatosis—are omitted. On the other hand, speculation and personal opinion on controversial clinical subjects, clearly indicated as such, are generously included.

Calcium Homeostasis

The serum calcium level is one of nature's biologic constants. Normally, it varies little from species to species, with the seasons or time of day, and only slightly between the sexes. As early as 1907, Erdheim[5] described the calcioprotective law, stating that nature protects the serum calcium level at the expense of bone. Erdheim showed that in experimental rickets the already

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demineralized bone is compromised further by parathyroid overfunction. It is now clear that the parathyroid hyperplasia of rickets or osteomalacia is the natural consequence of hypocalcemia. A fall in serum calcium levels stimulates parathyroid secretion; conversely, hypercalcemia turns it off.[6] But this simple, readily demonstrable feedback mechanism by itself cannot explain the precise, minute-to-minute control of the serum calcium level. If one removes the parathyroid glands of a dog, it takes at least 150 minutes before the serum calcium level falls.[7] Clearly, the previously secreted parathyroid hormone is still acting several hours later. As a consequence, it follows that, if the parathyroid feedback were the only control of the serum calcium level, each fall would cause a prolonged and hypercalcemia rise. Conversely, each rise above normal turns off the gland, but cannot promptly lower the calcium level to normal.

Copp's[8] discovery of calcitonin, which lowers serum calcium levels promptly, slightly and briefly in response to hypercalcemia, provides the missing link necessary to explain the precise, rapid control of the serum calcium level. Parathyroid hormone is the coarse adjustment; calcitonin is the fine adjustment. Parathyroid hormone acts by mobilizing calcium from the large bone reservoirs; calcitonin inhibits this process. What this hormone is doing in the ultimobranchial glands of elasmobranchs,[9] which have cartilaginous rather than osseous skeletons, is unknown. Its presence in this species suggests other thus far undefined actions.

In mammals, the antiosteolytic action of calcitonin causes serum calcium and phosphate levels both to fall. The precise balance of parathyroid versus calcitonin maintains the normal serum calcium level.

Role of the Sex Hormones

While parathyroid hormone and calcitonin are the only hormones known to have a feedback relationship to serum calcium levels, they are not the only hormones to control calcium equilibrium between gut, blood, bone, urine and feces. It has long been known that estrogens and androgens produce positive calcium balance.[10] Kinetic analysis shows that their mechanism of action on bone is not, as originally thought, anabolic, but anti-catabolic.[11-18] During their administration, calcium balance becomes positive, but, surprisingly, the rate of bone accretion does not rise; it actually falls. Therefore, the gain in calcium cannot be the result of increased bone formation but can only be the consequence of decreased bone breakdown. Their action is therefore qualitatively similar to that of calcitonin.

This mechanism, previously shown by indirect means, has recently been confirmed directly by Riggs, Jowsey and their co-workers,[19] using quantitative microradiography of iliac crest biopsy specimens in human postmenopausal osteoporosis. This important action has also been implicated indirectly in normal women and in patients with postmenopausal osteoporosis, breast cancer and acromegaly. Like calcitonin, estrogens and androgens lower serum calcium and phosphate levels.[20-24] Conversely, the serum phosphate level is raised in osteoporosis, breast cancer and in acromegaly.[21,25,26] It is likely that the slight lowering of normal serum calcium levels of women between puberty and the menopause also reflects the braking action of endogenous estrogens on osteolysis.[27-29]

Importance of Normocalcemia

The elaborate protection of the serum calcium level throughout the animal kingdom emphasizes the importance of the physiologically active calcium ion concentration. Until now this fraction has not been readily measurable. The advent of calcium electrodes may alter this situation. It should be borne in mind, however, that the ionic moiety is in equilibrium with the protein-bound fraction so that normally about half of the total serum calcium is in the free form. One cannot simply insert a calcium electrode in a random serum specimen at room temperature and determine the biologically significant calcium ion concentration. Factors known to influence the equilibrium between free and protein-bound calcium (temperature, pH, ionic strength, and quantity and quality of serum proteins)[30] require careful handling of serum or plasma specimens for meaningful calcium electrode measurements.

Clinically, the importance of the serum calcium level lies in its effect on neuromuscular irritability and central nervous system activity. A fall of 15 percent or more produces neuromuscular hyperirritability manifested as tetanic spasms of skeletal muscle, and seriously impairs mental processes. A similar rise inhibits smooth muscle contractility, especially in the gastrointestinal tract, causing anorexia, nausea, vomiting, constipation, ileus and abdominal pain. Moderate hypercalcemia inhibits the action of antidiuretic hormone on the distal renal tubule leading to hyposthenuria, nocturia, polyuria, thirst and dehydration.[31,32] Greater rises may precipitate uremia and central nervous system symptoms such as lethargy, somnolence, psychosis and coma. The nonspecificity of the individual symptoms of mild hypocalcemia and hypercalcemia may delay recognition of the underlying chemical abnormality until the typical symptom complex is fully developed, unless serendipity leads to a screening panel of blood chemistry.[33,34]

Adrenocorticosteroids

Like the gonadal steroids, adrenocorticosteroids have powerful effects on calcium homeostasis. It has long been recognized that Cushing's syndrome is characterized by a specific type of bone depletion. The osteoporosis of Cushing's syndrome, endogenous or exogenous, differs from that of postmenopausal osteoporosis in distribution, kinetics, and roentgen appearance of the involved bone. Unlike postmenopausal osteoporosis, the type induced by corticoid overdose often leads to rib fractures.[35] Like postmenopausal osteoporosis, Cushing's disease often involves the vertebrae, but their roentgen appearance is quite different; eburnation, or marginal thickening of the superior and inferior vertebral plates, characterizes Cushing's syndrome,[36,37] but not postmenopausal osteoporosis.

The most perplexing feature of the action of cortisone on bone is that an agent which causes severe skeletal breakdown, the mechanism which most commonly causes hypercalcemia, is itself extremely effective in correcting many kinds of hypercalcemia. This latter action has been well documented in the hyperosteolytic hypercalcemias of malignant disease and thyrotoxicosis as well as in those due to excessive intestinal absorption of calcium—for example, vitamin D intoxication and sarcoidosis.

It has recently been demonstrated that glucocorticoids inhibit the conversion of vitamin D to its biologically active forms.[38] This inhibition may contribute to the antihypercalcemic effects of these agents, but cannot by itself explain cortisone's antihypercalcemic efficacy. Cortisone also lowers normal serum calcium levels in man[21] and in rats.[39] This effect is similar to the action of calcitonin or of estrogens and androgens. In organ culture, cortisone prevents the osteolytic effects of vitamin A or of antiserum.[40]

These paradoxic effects, osteolytic on the one hand and antihypercalcemic on the other, can be integrated into a unified but heretical working hypothesis. It is tempting to speculate that the primary action of cortisone on bone is *anabolic* as shown in organ culture, in the effect on the normal serum calcium level, in hypercalcemia, in the roentgen appearance of the vertebral plates, and in their initial stimulation of skeletal dynamics. It has been shown experimentally both in man and in rats that in the absence of the parathyroids, corticoids conserve rather than waste calcium and phosphate.[41,42] It therefore seems possible that the calcium-wasting effect of corticoids may be mediated by the parathyroids in response to the fall in serum calcium these agents produce. Direct measurements of parathyroid hormone during corticoid administration have been made too rarely for direct assessment of this hypothesis.

Thyroid

Like the corticosteroids, thyroid hormones in excess are potent catabolic agents. This action is well shown by the hypercalcemia and hypercalciuria of thyrotoxicosis. Histologically, the bone shows very severe osteoporosis, even osteitis fibrosa.[43] Clinically, this osteoporosis is not apt to produce skeletal symptoms except in postmenopausal women.[44] Here, however, the distribution of the osteoporosis, involving ribs and skull, which are not so often visibly involved in postmenopausal osteoporosis, may suggest the diagnosis. In addition, correction of thyrotoxicosis alone may stop the fractures. In physiologic amounts, thyroid is essential both for maturation and for normal transfer of calcium from the serum to bone. Failure of this transfer in myxedema may cause hypercalcemia.[45] Thus, both hypo- and hyperthyroidism can cause hypercalcemia, though by different mechanisms.

Growth Hormone

The actions of the pituitary growth hormone on calcium metabolism are complicated. Like thyroid, growth hormone is essential for normal skeletal growth and may be useful in augmenting this process both in growth deficiency[46] and normal states.[47] In excess, however, growth hormone causes hypercalciuria,[48] probably for the most part because of its effect upon the renal tubule, though excessive osteolysis can also be inferred.[42]

Vitamin D

The last endogenous humoral agent in this array of calcium-active agents is vitamin D. In physiologic amounts—500 International Units (IU) a day—vitamin D acts on the intestinal tract to promote calcium absorption. In pharmacologic doses—for example, 50,000 to 150,000 IU per day—it directly lyses bone to release calcium. Pharmacologic doses also act on the renal tubules to lower tubular reabsorption of calcium so that hypercalciuria may occur even in the presence of hypocalcemia.[49,50] Provitamin D_3, or 7-dehydrocholesterol,[51] is made in the skin and metabolized, under the influence of ultraviolet irradiation, to cholecalciferol (vitamin D_3). In this form, vitamin D_3 is inert until activated in the liver and intestine.[52] The best established active metabolic product, 25-hydroxycholecalciferol (25-OH-D_3), directly and rapidly lyses bone in organ culture.[53] As Avioli and his group have shown, activation of vitamin D_3 to 25-OH-D_3 is deficient in steatorrheas, uremia, and after corticoid administration.[38] The intestinal malabsorption of calcium, which characterizes the steatorrheas and uremia, can be explained by failure of this mechanism. The secondary hyperparathyroidism of osteomalacia and of uremia follow naturally. In contrast, the pathogenesis of the peculiar type of osteoporosis—*not* osteomalacia—which characterizes Cushing's syndrome remains unexplained.

Disorders of Calcium Metabolism

Because *hypercalcemia* can cause serious, even fatal, acute damage or may insidiously compromise renal function, it is of great clinical importance. Interest in hypercalcemia has escalated, probably because of better availability of accurate calcium determinations, as well as enthusiasm for new and resurrected methods of treatment. Severe hypercalcemia is a medical emergency and requires rapid recognition and control. Chronic hypercalcemia too is damaging. In both types, correction of the underlying cause is the treatment of choice, but in the acute form emergency measures are life-saving. If the serum calcium level is moderately elevated, say to no more than 12.5 mg per 100 ml, hydration alone is corrective in most hypercalcemias other than hyperparathyroidism.[54] Conversely, mild hypercalcemia may be exacerbated by dehydration, sometimes to severe or even fatal levels. Perhaps dehydration is the reason why thiazides exacerbate the hypercalcemias of hyperparathyroidism or of malignancy.[55-57] In all types of hypercalcemia, hydration is the first line of defense. Sodium-containing solutions are particularly effective.[58] As was pointed out by Walser, increasing the serum sodium level, where feasible, is in itself a powerful way to stimulate calcium excretion.[59] In most hypercalcemias other than hyperparathyroidism, pharmacologic doses of glucocorticoids are also highly effective, correcting hypercalcemia in most cases of vitamin D intoxication, sarcoidosis and thyrotoxicosis, and in about half those of malignant disease. Corticoids are less effective in hyperparathyroidism, perhaps in 10 percent of the type due to parathyroid adenoma[60] and in about 20 percent of cases where parathyroid hormone is formed ectopically by a "non-endocrine" cancer.[61] Other emergency measures such as intravenous administration of sodium sulphate[62] and hemodialysis[63] are of transient but sometimes life-saving value.

While phosphate administration, either oral or intravenous, is highly effective in lowering serum calcium levels, it may be extremely dangerous because of ectopic calcification, except in the presence of phosphate depletion. On the other hand, this form of treatment is probably safe and may be the treatment of choice where hypercalcemia is accompanied by severe hypophosphatemia following a successful renal transplant, in the diuresis following renal shutdown,[64] or in some cases of hyperparathyroidism.[65,66] Calcitonin has been reported transiently effective in correcting hypercalcemia in a few cases of various causes.[67-70] Because of its brevity of action, it must be injected frequently in a gelatine menstruum. Its use is still investigational and should be restricted to those cases in which the cause cannot be corrected and the hypercalcemia controlled by standard procedures such as hydration and corticoid therapy.

Drastic Treatment of Hypercalcemia

In most cases, it is good medicine to ascertain the cause of hypercalcemia and correct it, especially in primary hyperparathyroidism, milk-alkali syndrome, sarcoidosis, hypervitaminosis D, thyrotoxicosis, post-uremia phosphate depletion, or controllable malignant diseases. Where this is not feasible, or where the underlying cause cannot be readily corrected, as in widespread malignant disease, and where hydration and corticoids alone do not control hypercalcemia, other measures must be considered. The use of cytotoxic antitumor agents to treat hypercalcemia, originally shown by Myers for diazo-oxo-norleucine (DON)[71] and then for methotrexate,[72] has recently been extended to actinomycin[73] and to mithramycin.[74,75]

These agents need not be given in toxic doses, nor do they affect hypercalcemia by controlling tumor growth. For example, mithramycin also lowers the elevated serum calcium level of hyperparathyroidism.[75] Moderate doses of cytotoxic agents—for example, 500 mg of 5-fluorouracil intravenously—are as effective and less toxic.[76] It is likely that these agents act by inhibiting osteocytic osteolysis, one of the mechanisms which supports the normal serum calcium level. Before taking council of despair and using desperate measures, the physician should remember that all the body's homeostatic mechanisms favor the patient and that most hypercalcemias other than hyperparathyroidism respond to hydration and corticoids.

"Tertiary" Hyperparathyroidism

It is not surprising that the hypercalcemia which sometimes follows successful renal transplantation has been equated with hyperparathyroidism. Parathyroid hyperplasia and hyperfunction are features of severe renal insufficiency,[77,78] and the combination of hypercalcemia and hypophosphatemia strongly suggests hyperparathyroidism. The occasional occurrence of parathyroid adenomas in patients with previous causes for secondary hyperparathyroidism has led to the attractive concept of autonomous or "tertiary" hyperparathyroidism. This term, independently coined by Walter St. Goar in 1963,[79] has so captured the imagination that the German author, Kuhlencordt,[80] has recently claimed priority for his compatriot Bock, who used this term in 1957.[81] Regardless of who published first, "tertiary" hyperparathyroidism is probably a myth. It is by no means certain that the incidence of parathyroid adenomas in renal insufficiency or in steatorrhea[82-86] is more frequent than can be accounted for by coincidence. In most of the hypercalcemias which follow renal transplantation or renal shutdown, parathyroid hormone levels are low or absent.[87,88] In well controlled series the hypercalcemia following renal transplantation is infrequent and of multiple causes.[87-89] We have seen post-transplant hypercalcemia caused by the use of calcium salts as antacids, which are commonly used in these patients to counteract the gastric effects of corticoids that are being taken by patients as part of their immunosuppressive therapy. Some hypercalcemias are due to mobilization of ectopic calcium phosphate deposits, probably as a consequence of postcorrectional hypophosphatemia.[64] The hypophosphatemia following successful renal transplantation probably results from a combination of bone healing, increased phosphate clearance, lowering of tubular reabsorption of phosphate by corticoids[21] and use of aluminum antacids which bind dietary phosphate.[90] The few parathyroid adenomas found in uremic patients are probably either coincidental or the cause, rather than the result, of uremia. It is a fundamental error to equate hypercalcemia with hyperparathyroidism.

Medullary Carcinoma of the Thyroid

Medullary carcinoma is a tumor of the calcitonin-producing parafollicular cells, which in submammalian species are found in the ultimobranchial body. Calcitonin overproduction is now well established as a feature of medullary carcinoma of the thyroid.[91-93] Earlier suggestions that excess calcitonin might cause pseudohypoparathyroidism,[94,95] a thesis inconsistent with the hyperphosphatemia of pseudohypoparathyroidism, have now been disproved.[96] Despite secretion of large quantities of calcitonin, medullary carcinoma rarely causes hypocalcemia, probably because of the efficiency of homeostatic defenses. One of these responses, parathyroid stimulation, may account for part of Sipple's triad: medullary carcinoma of the thyroid, hyperparathyroidism and pheochromocytoma.[97] Patients with medullary carcinoma as part of this triad are noted to have a particular facies.[98,99] Some of the other clinical manifestations of medullary carcinoma, such as diarrhea, may result from secretion of prostaglandins.[100] Ectopic secretion of calcitonin by nonendocrine tumors, first suggested by Prader,[101] has now been established by Milhaud et al[102] in a case of bronchial carcinoid. Whether this is truly an example of ectopic production or will characterize such tumors remains to be seen.

Hypoparathyroidism

This condition occurs as an inadvertent consequence of thyroidectomy, for unknown cause (idiopathic), or in association with brachydactyly, short stature, round face and resistance to parathyroid hormone (pseudohypoparathyroidism). Renal resistance to parathyroid hormone in pseudohypoparathyroidism has been traced to absence of renal adenyl cyclase.[103] Serum parathyroid hormone levels are nil in the first two forms and greatly elevated in pseudohypoparathyroidism. Roentgen evidence of elevated parathyroid hormone levels may be found as subperiosteal resorption of the phalangeal cortex.[104,105] Why this resorption fails to correct hypocalcemia is unexplained. In pseudohypoparathyroidism, elevated serum parathyroid hormone (PTH) levels quickly revert to normal when vitamin D restores normocalcemia.

Treatment of Hypoparathyroidism

Since hypocalcemia and hyperphosphatemia both must be corrected to control tetany and to prevent metastatic calcification, classical therapy used to include calcium-mobilizing sterols (vitamin D_2, vitamin D_3, and dihydrotachysterol), supplemental calcium, a low phosphate diet and oral aluminum salts to bind dietary phosphates. It has subsequently become clear that adequate doses of vitamin D suffice to restore normocalcemia without added calcium supplements. In addition, patients whose hypoparathyroidism is well controlled by vitamin D can excrete oral phosphate loads normally, so that a low phosphate diet is not necessary.[106] Thus, in most patients, oral calcium salts and low phosphate diets serve only to complicate the therapeutic regimen and favor iatrogenic hypercalcemia.

In the vast majority of cases of hypoparathyroidism, vitamin D alone provides adequate therapy. It raises the serum calcium and lowers the serum phosphate level to normal. Adequacy of treatment is judged entirely by the blood chemical levels. Observing the urinary calcium excretion (Sulkowitch test) as a way to evaluate adequacy of treatment is misleading since vitamin D produces hypercalciuria before the serum calcium level rises to normal.[49-51] It must be borne in mind that vitamin D takes six to twelve weeks to obtain its full effect; that about 95 percent of patients with hypoparathyroidism achieve normal serum calcium and phosphate levels when treated with doses of 50,000 to 150,000 units a day; and that the actions of the agent may persist six to twelve *months* after administration has been discontinued. Failures of therapy are most commonly due to use of a poor preparation,[107] since vitamin D is a labile material with a rather short shelf life.* Vitamin D resistance in hypoparathyroidism is rare; when encountered, dihydrotachysterol is reported to be effective.[108] Some preparations, formerly used widely and with rather poor results, have been shown to contain no dihydrotachysterol.[109] Fear that the use of large doses of vitamin D in pregnant women with hypoparathyroidism may result in fetal cardiovascular malformation[110] happily has not been borne out in practice.[111]

Pitfalls in the Diagnosis Of Hypoparathyroidism

Because of the long action of vitamin D, it may be very difficult to ascertain whether the original diagnosis of hypoparathyroidism in the vitamin D-treated patient was in error. Following any surgical procedure under general anesthesia, the serum calcium level drops, sometimes as low as 7.8 mg per 100 ml and the serum phosphate level rises.[112-114] If the operation was a thyroidectomy and the patient has Chvostek and Trousseau signs from anxiety or hypocalcemia, these phenomena may lead to an incorrect diagnosis of hypoparathyroidism. The nonspecific hypocalcemia following general anesthesia subsides in a few days, while that of hypoparathyroidism persists or becomes worse. Early vitamin D treatment is both irrational and misleading since the onset of action is slow and the long action requires months of withdrawal to ascertain whether the blood calcium level is maintained by endogenous parathyroid hormone. For these reasons it is advisable to treat postoperative hypocalcemia with short-acting intravenous and oral calcium preparations rather than vitamin D and to defer diagnosis for

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*In reviewing this manuscript, Dr. John Eager Howard called my attention to the fact, unknown to me, that vitamin D, while unstable in crystalline form is good for at least 50 years in oil or propylene glycol. Therefore, our unhappy experience with generic vitamin D is probably due to poor preparations rather than instability. Our troubles disappeared in 1961 when The Upjohn Company generously supplied us with vitamin D (Calciferol) Geltabs®, 50,000 I.U. (1.25 mg.). Of 150 patients with hypoparathyroidism, all but four were rendered normocalcemic, or nearly so, by doses of 50,000 to 150,000 I.U. daily. Three years ago, The Upjohn Company temporarily discontinued this preparation. Patients who had been well controlled were now hypocalcemic or hypercalcemic while receiving the same dose formulated by other manufacturers. When Upjohn's vitamin D was again used, good control was again achieved. This convinced us of the importance of using a well calibrated standard preparation rather than prescribing generic vitamin D. It is likely that alleged failures of vitamin D in renal osteodystrophy, osteomalacia and hypoparathyroidism result from the use of poor preparations.

at least a week. In the vitamin D-treated patient, two techniques may facilitate demonstration of normal parathyroid function. One of these is the response to corticoids, which rapidly precipitate tetanic levels of hypocalcemia in patients with hypoparathyroidism.[115,116] The other is the less generally available parathyroid hormone assay; measurable parathyroid hormone in the serum serves to exclude hypoparathyroidism. Otherwise vitamin D may have to be withdrawn for a year or more before the serum calcium levels fall. It is a fundamental mistake to equate tetany with hypocalcemia, or hypocalcemia with hypoparathyroidism.

Hyperparathyroidism

Diagnosis. Hyperparathyroidism, once rare, is now recognized relatively often because of the general availability of accurate calcium determinations. It must be reemphasized that hypercalcemia is not to be equated with hyperparathyroidism, but that hypercalcemia is virtually essential for the diagnosis. Normocalcemic hyperparathyroidism is rare; parathyroid exploration in normocalcemic subjects leads to many "negative operations." In proved hyperparathyroidism, hypercalcemia may be masked temporarily by a high phosphate intake,[65,66] by concomitant intestinal malabsorption,[86] by acute pancreatitis,[117] or by an infarct of a parathyroid adenoma.[118] Of these, the most common is a high phosphate intake, for some patients with hyperparathyroidism, like Curt Richter's parathyroid extract-treated rats,[119,120] have an increased appetite for phosphate. A low phosphate diet rapidly restores hypercalcemia if it has been obscured by a previous high phosphate intake.[120-122]

Recognition of those patients whose hypercalcemia is due to hyperparathyroidism can be accomplished in numerous ways, the least desirable of which is surgical "exploration." Hypophosphatemia, while helpful when present, occurs in less than half the cases.[120,123] Exclusion of other causes of hypercalcemia is inadequate, since 15 percent of patients with proved hyperparathyroidism simultaneously harbor additional diseases known to cause hypercalcemia.[60] In my experience, the best available diagnostic combination is that of hypercalcemia plus hyperphosphaturia (increased phosphate clearance or low tubular reabsorption of phosphate), in the absence of the few other conditions known to cause this combination (sarcoidosis, myeloma, or vitamin D overdose).[124-126] Since hypercalcemia of other causes turns off the parathyroid, the combination of measurable serum parathyroid hormone levels and hypercalcemia is diagnostic of hyperparathyroidism. This constellation occurs both in primary hyperparathyroidism (parathyroid adenoma or hyperplasia) and in the syndrome where hyperparathyroidism arises ectopically from a "non-endocrine" cancer. Separation of parathyroid from ectopic causes of hyperparathyroidism may range from easy to impossible. In some cases, hypercalcemia may be the first manifestation of the underlying tumor. Other evidences of malignant disease, such as anemia, an elevated alkaline phosphatase level in the absence of roentgenologically visible subperiosteal resorption of the phalangeal cortex, response of hypercalcemia to corticoids, and serum chloride levels below 102 mEq per liter, should make one think of the ectopic syndrome.[61]

To Treat or not to Treat. The most difficult question to answer with the mild—often asymptomatic—kind of hyperparathyroidism seen nowadays is whether operation is really necessary. The severe hyperparathyroidism recognized from 1930-1950 often went on to uremia and hypertension despite removal of the causative parathyroid tumor.[127,128] The prognosis of milder hyperparathyroidism is not yet known.[123] Operation in borderline cases is often unproductive.[129] Since hypercalcemia insidiously damages the kidney and can become acutely life-threatening on dehydration or immobilization, clear-cut hyperparathyroidism should probably be corrected surgically in almost all cases. Where the condition is mild, asymptomatic and associated with other major disease in the elderly, one may consider non-surgical treatment by hydration, phosphate administration and the use of anti-osteolytic steroids.[130] This is probably an uncommon situation and the treatment appropriate in only a small proportion of carefully considered cases where the patient can be followed closely and frequently.

Renal Osteodystrophy

The skeletal complications of uremia are the summation of the consequences of three processes: (1) *calcium malabsorption,* due to failure of activation of vitamin D leading to hypocalcemia and to (2) *secondary hyperparathyroidism,* as well as (3) *hyperphosphatemia* due to impaired filtration of phosphate, causing abnormal deposits of calcium phosphate in bone (osteosclerosis) and soft tissues. Therefore, osteomalacia, osteitis fibrosa and osteosclerosis may co-exist in varying combinations.[131-135] Since the fundamental defects are calcium malabsorption[136,137] and hyperphosphatemia, pharmacologic doses of vitamin D or dihydrotachysterol, together with low phosphate diets and aluminum hydroxide, can and do reverse the process.

Before the advent of hemodialysis and renal transplantation, renal osteodystrophy was a terminal event in uremia, indicating a very short life expectancy. Nonetheless, when carefully treated with adequate doses of vitamin D or dihydrotachysterol (along with measures to lower the serum phosphate level), osteodystrophy was regularly reversible.[76,131,138] Hemodialysis and renal transplantation have altered the picture. If chronic hemodialysis is carried out with calcium concentrations of less than 6 mg per 100 ml of bath fluid, secondary hyperparathyroidism may be seriously aggravated; with higher concentrations, ectopic calcification may be precipitated.[139-142] The success of dialysis and renal transplantation has prolonged life so that, in many cases, renal osteodystrophy and ectopic calcification have come to dominate the clinical picture.

As discussed above (under the heading *Hypercalcemia*) there has been a recent tendency to overemphasize the value of therapeutic or even prophylactic parathyroidectomy. This operation of course necessitates replacement therapy with pharmacologic doses of vitamin D—which, in most cases, is successful without parathyroidectomy. Our experience, like that of others, is that the parathyroids are not autonomous in uremia, that hyperparathyroidism resolves after successful renal transplantation[87,88,142-144] and that post-transplant hypercalcemia is infrequent, not often associated with increased serum parathyroid hormone levels, and usually correctible by innocuous treatment. In the opinion of this reviewer, parathyroidectomy should be considered only after an adequate trial of vitamin D or in the event that the patient has both renal insufficiency and a parathyroid adenoma (coincidental primary, or so-called tertiary, hyperparathyroidism).

One possible reason for failure of vitamin D therapy is the lability of this sterol, leading to use in some cases of preparations with little or no pharmacologic activity.* This phenomenon is well known to physicians experienced in the treatment of hypoparathyroidism and is easily avoided by using a good preparation.

Kaye et al reported that dihydrotachysterol uniformly arrested hyperparathyroid bone disease in patients undergoing hemodialysis[145] and seriously questioned the desirability of parathyroidectomy in patients undergoing chronic dialysis. Dihydrotachysterol may be more easily controlled than vitamin D in patients with renal insufficiency because of its more rapid effect and shorter period of action. The danger of hypercalcemia from overdose of vitamin D or dihydrotachysterol is real, and in uremic patients can be especially hazardous because of the deleterious effects of hypercalcemia on renal function. Frequent monitoring of serum calcium levels is essential.

The renal insufficiency which follows prolonged and severe hypercalcemia is often associated with special forms of metastatic calcification. Since filtration of phosphate is impaired, a rise of serum phosphate levels occurs in all forms of severe uremia.[146] In the presence of hypercalcemia, a very high (Ca x P) product occurs, leading to calcium phosphate deposition in vital organs.[147] Rapid correction of the acidosis of this form of uremia favors further precipitation of calcium phosphate, especially in the pulmonary alveoli, producing a clinical picture similar to that of pulmonary edema. This complication is usually fatal; it is more easily prevented than treated, especially by avoiding a rapid rise of arterial pH and by correcting hyperphosphatemia.

Osteoporosis

Heterogeneity of osteoporosis. Evaluation of medical literature on osteoporosis is extremely difficult because of confusion about types of patients treated, criteria for diagnosis, the type of osteoporosis present—if any—and difficulties in obtaining criteria for efficacy of treatment. It is important to recognize that there are three common heterogeneous types of osteoporosis with different pathophysiologic features and different clinical and roentgen appearances, for which different kinds of treatment may be indicated.

1. The *osteoporosis of disuse* can be localized or generalized, depending on the area of the body immobilized. While kinetic studies show an increase in the bone accretion rate,[15] suggesting that

*See footnote on page 33.

accelerated osteolysis is the most important feature, it is also reasonable to believe that immobilization inhibits osteoblastic activity. With the converse — exercise — there is acceleration of bone accretion and bone density.[148,149] With immobilization the serum alkaline phosphatase level, the indicator of osteoblastic activity, falls.[150] An important feature of the osteoporosis of immobilization is that it often aggravates preexisting osteoporosis of other causes. Whenever possible, cessation of immobilization, or at least its reduction as much as feasible, is indicated.

2. By far the most common type of osteoporosis is the *post-menopausal* variety. The reason to implicate the menopause rather than old age[151] is based on its great frequency in women and relative rarity in men, and the fact that it can rarely be recognized less than ten years after a spontaneous menopause, or three years after oöphorectomy.[76] In addition, congenital absence of ovaries (gonadal dysgenesis) is almost universally accompanied by osteoporosis except in the variety where the interstitial cells secrete testosterone,[152] where osteoporosis is notably absent.[153]

3. The third large group where the etiologic delineation of osteoporosis is clear is that *due to excess glucocorticoids.* Previous arguments as to whether the action is catabolic or anti-anabolic[154] can now be settled by evidences that both processes occur at different times. In the first few weeks of administration of large doses of corticoids, bone accretion is greatly increased at the very time that calcium balance is strongly negative.[14] Later, or in spontaneous Cushing's disease, the bone accretion rate is low.[148] As suggested above, it is possible that the early catabolic effect may be mediated by the parathyroid, although it must be admitted that the bone lesion does not resemble that of hyperparathyroidism. Perhaps corticoids modify this appearance. The low serum phosphate levels and low tubular reabsorption of phosphate produced by corticoids[21,155,156] are consistent with parathyroid overfunction.

Differential Diagnosis. In addition to the three common types of osteoporosis, a disproportionate number of metabolic studies have been reported on the relatively rare idiopathic variety. Unfortunately, clinical investigation of this disorder has often been extrapolated to the therapy of other types of osteoporosis. It seems, also, that much osteoporosis exists only in the eye of the beholder. In our Bone & Stone Clinic, it is common to see patients referred for treatment of osteoporosis in whom the diagnosis turns out to be carcinomatosis, myeloma, juvenile epiphysitis, vertebral osteophytosis, osteogenesis imperfecta, osteomalacia, or no demonstrable bone disease at all. In the latter, roentgen evidence for osteoporosis is often artifactual. The most common artifacts are increased radiolucency due to excess kilovoltage or milliamperage, and the false appearance of biconcave vertebrae produced by an improper positioning of the roentgen tube. A common clinical cause for error is misinterpretation of a transient backache (who hasn't had one?). The backache of osteoporosis is usually long-standing, non-radiating, non-tender (except during acute fracture) and situated in the lumbar or lower thoracic vertebra.

Criteria for Diagnosis. In reviewing reports on treatment of osteoporosis, it is often difficult to ascertain whether the patients did indeed have this condition. In practice also, to avoid treatment of a condition which is not there, it is desirable to have rigorous, objective criteria. These will necessarily be evidences of advanced osteoporosis, since earlier loss of bone tissue cannot be detected clinically or by routine radiology, but only by sophisticated bone density techniques.[157-159] Urist[160] and I[161] have independently derived the same diagnostic criteria based on radiological evidence of mobilization of trabeculae and vertebral deformity. Since the trabeculae or spongiosa are mobilized to a greater degree than the cortex, the vertebra in advanced cases gives the appearance of a hollow box. Earlier, the branching (secondary) trabeculae are lost. In an intermediate stage, the trabecular population is so reduced that one can actually count the primary trabeculae as he scans a lateral film of a vertebra. This appearance is in contrast to that of normal spongiosa which shows uncountable, intricately woven trabeculae. Because of the loss of spongiosa, the cortex, which is involved to a lesser degree, may actually give the false appearance of increased density. This leads to increased contrast between the cortex and spongiosa. In the post-menopausal variety of osteoporosis, the cortex is thin[158,162] but uninterrupted. Erosion of the cortex should make one think of malignant disease. In the osteoporosis of Cushing's disease, the superior and inferior plates are actually thickened or eburnated.[35-37] This appearance is pathognomonic of corticoid-induced osteoporosis. Various types of vertebral deformity may be seen. One is biconcavity due to bowing of the superior and inferior vertebral plates by the pressure of the intervertebral discs. Localized invagination of a disc through the plate into the body of the vertebrae may occur; these are Schmorl's nodes. They are not restricted to osteoporosis, but occur in many vertebral diseases or developmental anomalies. Later wedge or compression fractures may occur. In osteoporosis the apex of the wedge fracture is anterior. Posterior wedging strongly suggests a different disease such as cancer, Paget's disease or trauma. Unlike fractures of other causes, vertebral fractures in osteoporosis generally do not cause neurologic complications. Naturally, immobilization should be minimized in any osteoporotic patient. In its earliest phase, only the weight-bearing vertebrae, from the eighth thoracic down, show involvement. A solitary fracture in a vertebra above this level strongly suggests a different cause, such as cancer, myeloma, epilepsy, electric shock therapy,[163] or trauma. Later, of course, when the entire spine is visibly involved, wedging may occur in the upper thoracic vertebrae as well. Fractures and kyphosis cause loss of stature, which is a useful index of new fractures.[164] Rather than obtain x-ray films of the entire spine at each examination, it is desirable to record exactly the patient's height and span. "If we measure from the sole of the foot to the top of the head, and apply the measure to the outstretched hands, the breadth will be found equal to the height" (M. Vitruvius Pollio, 27 B.C.).[165] In the absence of other conditions associated with decrease in height compared with span (arachnodactyly, hypogonadism or normal Negro proportions), vertebral fractures reduce height without affecting the span. Accurate measurement at each examination is a practical way of determining the presence of a new fracture.

Other conditions. With the diagnostic criteria listed here, one will not recognize early osteoporosis nor can it be recognized at present without sophisticated bone density techniques or bone biopsy. Onset of severe "osteoporosis" too soon after a normal menopause and involving too many vertebrae should make one think of neoplasm, osteogenesis imperfecta, or other disease. In the mild form of osteogenesis imperfecta, fractures stop at puberty and resume at the menopause. The presence of blue sclerae and spindly long bones may help in the diagnosis. Osteoporosis may co-exist with other causes of back pain, such as spondylolisthesis, vertebral osteophytosis, and acute back sprains. The pain of these disorders should not be expected to respond to measures directed at controlling the osteoporosis.

Treatment of the Osteoporoses. In recent years multiple treatments have been suggested for osteoporosis. Bearing in mind that osteoporosis comprises a heterogeneous group of disorders, it is not surprising that no one treatment provides a panacea. For postmenopausal osteoporosis, estrogens and androgens have been advised (see below). Whether estrogens should be used prophylactically depends somewhat on the philosophy of the physician—whether he prefers to prevent or to treat disease. Davis et al[166] and the Meemas[162] have provided densitometric evidence that estrogen therapy significantly retards loss of bone substance in postmenopausal women. The use of estrogens and androgens in men, who far less commonly show osteoporosis by the criteria listed above, has been shown ineffective by the careful balance studies of Schwartz et al.[167] This group has shown that administration of large doses of calcium by mouth does indeed cause calcium retention, as previously reported by others.[168,169] Schwartz, however, pointed out that the calcium retention is not accompanied by phosphate retention, as it would be if bone mineral were being laid down.[167] Rose[170] denies that oral calcium produces positive calcium balance when carefully measured with chromium controls. He also notes that this treatment increases urinary calcium excretion and may precipitate renal calculi. Recently, Bartter and his co-workers[171,172] have studied the effects of intermittent calcium infusion to inhibit bone resorption in idiopathic osteoporosis. This investigation cannot be extrapolated to the therapy of either postmenopausal or corticoid-induced osteoporosis. Fluoride therapy has had a certain vogue based on the observation that inhabitants of areas with endemic fluorosis have dense bones.[173] The bone in fluorosis is not only dense, but brittle, and ectopic calcification—for example, painful peritendinitis calcaria—is common.[174] Since tea contains large amounts of fluoride, one might expect tea drinkers to be immune to osteoporosis, if this agent is really effective. Judging by the incidence of postmenopausal osteoporosis in the British Isles, I would guess that support for this thesis will probably not be forthcoming. Fluoride administration may produce slightly positive calcium balance[175] though this has been denied by Rose.[170] Although fluorosis is characterized by increased bone density, it is not yet clear whether fluoride therapy benefits patients with the osteoporoses. It is also well established that fluorosis has toxic effects on bone[176] and elsewhere. At present, therefore, induction of fluorosis in patients with the osteoporoses can only be considered investigational.

With all these divergent treatments, it is evident that there is some dissatisfaction with present treatment of the various kinds of osteoporosis. Not surprisingly, the advent of calcitonin has raised therapeutic hopes. Experimental evidence is that calcitonin, like estrogens and androgens, inhibits bone resorption but does not stimulate bone accretion. Calcitonin has been tried in several forms of experimental osteoporosis in animals, without effect,[177-179] although it has been shown to retard osteolysis in intact rats.[180] In osteoporotic man, preliminary data suggest some calcium-retaining effect, unfortunately accompanied by evidence of parathyroid stimulation.[181-183] As pointed out above, calcitonin and sex hormones have the same action on bone, so that therapeutic effects can be expected to be similar.

Estrogen Therapy of Postmenopausal Osteoporosis. The use of estrogens for their ability to reduce bone breakdown in postmenopausal osteoporosis is now time-honored. Perhaps the reason their efficacy has been called into question is that too much was expected. They do not form new bone, increase bone density, relieve the mechanical sequelae of fractured vertebrae or correct preexisting deformities such as kyphosis. It is established only that they prevent progress of the disease. In 1947 Reifenstein and Albright reported a beneficial effect of estrogens and androgens on calcium balance in women with postmenopausal osteoporosis.[10] In a retrospective study of Albright's patients, Henneman and Wallach[184] showed that prolonged treatment with estrogens stops fractures and loss of height. Clinically, it is impressive that most osteoporotic women given estrogens note relief of pain, usually in the third week of treatment. This desirable subjective effect, however, cannot be taken as evidence of efficacy. In a carefully controlled study, using the double-blind Latin square technique, Solomon, Dickerson and Eisenberg found similar relief of pain and induction of wellbeing with an estrogen and a psychoactive placebo, and even in half the patients treated with the inert placebo, lactose.[185] In this study it was shown that while the estrogen and androgen caused similar retention of calcium and of an exogenous strontium test load, the estrogen produced subjective wellbeing but the androgen did not. There was no connection between objective and subjective endpoints. In a twenty-year prospective study designed to compare the efficacy of estrogens with that of androgens and "anabolic" steroids (all weak androgens), various endpoints were sought.[186] It was found that relief of pain, reduction in urinary calcium or serum phosphate levels, induction of positive calcium balance and effects on skeletal kinetics, did not correlate with ability to prevent further fractures. The latter was therefore taken as the only conclusive evidence of objective efficacy. Obviously, such studies require long periods of observation, and the number of patients who can be studied is limited. The experimental design was that of the crossover, i.e. when a patient failed on one treatment or was unable to tolerate the agent, she was transferred to the other treatment group. In fact, however, the "crossover" ended in a one-way shift to estrogens, in large part because of the patients' intolerance of the androgenic effects of testosterone and its less androgenic "anabolic" derivatives. In twenty years of observation eight vertebral fractures occurred in 220 women receiving estrogens for 1,545 patient-years—a rate of five fractures per thousand patient-years. The vertebral fracture rate in 72 trials of androgenic-anabolic steroids for 202 patient-years was 40 per 1,000 patient-years, significantly worse than with estrogens ($p<0.01$). The minimal effective dose of estrogen was 1.25 mg of Premarin®, 50 μg of ethinyl estradiol, or 0.5 mg of stilbestrol daily for 25 days each month. Lower doses were ineffective in stopping vertebral fractures. Four of 220 women, who continued to have fractures on 1.25 mg of Premarin daily, required 2.5 mg of Premarin daily to prevent further fractures.

Cyclic Estrogen Therapy does not cause Cancer. In this study, too, the incidence of cancer was not increased by estrogen therapy. Because of the number of patients, their advanced age, and the number of years at risk, 18 cancers would normally have been expected. In fact, however, only six were seen and none of these was in the most common sites of female cancers, the cervix and breast. This study therefore showed no evidence that cyclically administered estrogens in usual doses act as a potent carcinogenic stimulus. Thus, estrogen therapy of postmenopausal osteoporosis is effective in stopping the progress of the disease and does not increase the risk of cancer.

Corticoid Induced Osteoporosis. It is sad to think that 20 years after the introduction of corticoids for their anti-inflammatory effect, and despite 40 years of recognition of the osteoporosis of Cushing's disease, no treatment has been established for this condition. A single report of carefully controlled balance studies by Sprague et al in 1950[187] and an important abstract by Henneman et al in 1955[188] on the calcium-sparing effects of estrogen and androgen in 28 cortisone-treated asthmatics are the only studies known to this reviewer. These fragmentary data suggest that estrogens may reduce corticoid-induced bone breakdown in women, and androgens that of men. Calcium therapy was found ineffective in experimental osteoporosis produced by cortisone in rabbits.[189] Here clearly is an area where studies on pathophysiology and clinical pharmacology, and a rationale for good therapy, are needed. Meanwhile, clinicians can only keep the dose of corticoids as low as possible and avoid long-term, high-dose treatment for trivial indications.

Paget's Disease

Paget's disease has recently come into the limelight because of rediscovery of the therapeutic benefit of antiosteolytic agents, in this case calcitonin, especially the very potent preparation from salmon ultimobranchial glands.[70,190-193] Paget's disease should probably not be called a disease in the majority of cases where it is found by accident, involves one or two bones and causes neither symptoms nor complications.

Pathophysiology. In its initial stages, best seen in the skull, it is characterized by a destructive process, miscalled osteoporosis circumscripta.[194] This destructive process spares the osteoblasts, causing a rise of alkaline phosphatase—unlike myeloma, which replaces osteoblasts and lowers the phosphatase level.[195] As a consequence, the resulting bony instability stimulates the osteoblasts to lay down more bone. Bony overgrowth in wild, unphysiologic patterns is seen on roentgenograms. Bowing and deformity occur in those few patients who go on to a very far advanced stage of the disease. The nature of the underlying destructive processes is unknown. Because Paget's disease is rare before the age of 40 and is associated with increased vascularity, arteriovenous aneurysms and increased cardiac output, a vascular cause is suggested. Immobilization of patients with advanced Paget's disease causes the alkaline phosphatase level to fall, interpreted as a decrease in osteoblastic activity; urinary calcium excretion rises, indicating increased bone breakdown.[196] Since the rate of formation and destruction in widespread Paget's bone is astronomical, the adverse effect of immobilization on osteoblastic activity in the face of increased or exaggerated bone breakdown can lead to serious consequences, both local and remote. One of these is fracture of the immobilized bone. Another is the metabolic consequence of rapid bone breakdown: hypercalciuria and perhaps hypercalcemia. Immobilization is sometimes enjoined inappropriately in these patients because of painful, incomplete cortical fractures (infractions) that occur on the convex surface of bowed long bones.[194] These should not be immobilized since the pain disappears spontaneously and immobilization often leads to a true fracture. The danger of hypercalcemia in immobilization of even very widespread Paget's disease is probably exaggerated. My records show 64 immobilized patients with Paget's disease in the last 22 years. Naturally, they were closely observed for fear of hypercalcemia. In fact, however, the only patients in whom this was detected also harbored parathyroid adenomas! Both the local and metabolic dangers of immobilization, on the other hand, are real. Fractures and hypercalciuria are common[197,198] and renal calculi are frequent in such patients.

Treatment. When it comes to therapy, it has been reported that corticoids inhibit both the skeletal and cardiovascular processes.[199] The doses, however, are large and toxic. Twenty years ago, we reported that estrogens regularly reduce urinary calcium excretion and alkaline phosphatase levels in women with Paget's disease and androgens do the same in men.[198,200,201] These observations were soon confirmed by others.[202,203] The pain, which characterizes approximately a third of our cases of Paget's disease, disappeared during this treatment. We were reluctant to make much of the effect on pain since it is well known that the pain of Paget's disease responds to almost any medical or surgical maneuver ever tried.[204] On the other hand the objective evidences of decreased alkaline phosphatase and urinary calcium excretion encouraged us to continue this treatment. While it is impossible to say that the course of the disease has been altered, pain has regularly been relieved and urinary calcium excretion has regularly declined. Similar results have been reported with aspirin,[205] fluoride,[206] calcitonin, and the toxic anti-tumor agent mithramycin.[207] The doses of estrogens used in women are the same as those used for postmenopausal osteoporosis—for example, Premarin® 1.25 mg, ethinyl estradiol 50 μg, or stilbestrol 0.5 mg daily for 25 days each month. In men testosterone cyclopentyl propionate (Depotestosterone®) or enanthate (Delatestryl®), 200 mg intramuscularly once a month reduce pain, calciuria and alkaline phosphatase levels. A similar antiosteolytic effect has been reported with porcine thyroid calcitonin[70,192,193] and with smaller doses of salmon ultimobranchial calcitonin.[190] Whether calcitonin injected frequently does anything that cannot be accomplished more easily by small doses of orally administered sex hormones remains to be seen.

"Be not the first by whom the new are tried,
Nor yet the last to lay the old aside."
—Alexander Pope: Essay on Man.

Trade and Generic Names of Drugs

Cortone® & Cortef®	cortisone
Diuril®	chlorothiazide
Hydrodiuril® & Esidrix®	hydrochlorothiazide
Mithracin®	mithramycin
Fluorouracil®	5-fluorouracil
Dihydral®	dihydrotachysterol
Amphojel®	aluminum hydroxide gel
Premarin®	conjugated estrogens (equine)
Estinyl®	ethinyl estradiol
Adeflor®	fluoride
Depo®-Testosterone Cypionate	testosterone cypionate
Delatestryl®	testosterone enanthate

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TOLERABLE MILK INTOLERANCE

How do you treat milk or lactose intolerance?

"We limit the intake to the amount tolerated. Milk intolerance is not an allergy. Most of the people are able to drink milk in cereal or in coffee; they can drink it in small amounts. I have them limit the amount of ice cream and milk chocolate to the amount that would cause any symptoms. They also limit intake of powdered drinks, like Ovaltine® and Kool-Aid®, which are high sources of lactose. If patients want to drink milk, they can drink it in small amounts—a fruit juice glass three or four times a day. It seems to help if they take it with meals because gastric emptying seems to be delayed and the lactose gets a chance to be digested by whatever enzyme is present. It also helps if they don't take it iced, if they don't drink it right from the refrigerator. Icing a beverage will increase small intestinal speed of transit so that if the lactose is iced, it goes by so quickly that it doesn't get digested. Some of the fermented products, like yogurt and true cultured buttermilk, can be taken because the lactose has been split to lactic acid; some low-lactose-content milks are also on the market."

—Theodore M. Bayless, M.D., Baltimore
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